Int. J. Cancer: **114,** 472–478 (2005)

Parental occupational exposures and Ewing's sarcoma

Lee E. Moore*, Laura Gold, Patricia A. Stewart, Gloria Gridley, Jacqueline R. Prince and Shelia Hoar Zahm

Division of Cancer Epidemiology and Genetics, NCI, NIH, DHHS, Bethesda, MD, USA

A case-control study of Ewing's sarcoma (ES) was conducted to search for occupational exposures associated with ES. The study consisted of 196 cases and 196 random-digit controls matched on geographical region, gender, ethnic origin and birth date. A questionnaire was administered to mothers of participants to obtain information on medical conditions, medications, and parental occupations during and after the index pregnancy. An occupational exposure expert coded jobs and industries for possible and probable exposure to selected occupational hazards. Risk of ES was increased with probable parental exposure to wood dusts during their usual occupation post pregnancy (odds ration [OR] = 3.2; 95% confidence interval [CI] = 1.1–9.2). Other exposures, including *a priori* suspected risk factors such as exposure to pesticides and farm animals, were not significantly associated with ES. A history of household pesticide extermination was associated with ES among boys aged 15 or younger (OR = 3.0; 95% CI = 1.1–8.1), but not among girls or older boys. Our results suggest that earlier reports of associations of ES with parental farm employment may have been describing risks associated with organic dusts encountered when working on a farm, rather than agricultural exposures or other farming related exposures.

Key words: Ewing's sarcoma; organic dusts; pesticides; childhood cancer

Ewing's sarcoma (ES) is a rare bone cancer, with an annual incidence rate of 2.9 per million in the U.S.[1] Although it can occur at any age, onset of ES occurs primarily in children and adolescents.[2–5] Unlike other bone cancers, ES is believed to originate from the neural crest[5] and has no animal model.[3–6] Males are at somewhat greater risk of developing ES, especially during adolescence, and Caucasian children are at much greater risk than African-American children.[1–4,7,8]

Little is known about the etiology of ES. Both genetic and environmental exposures have been considered. Previous research,[9–12] as well as earlier results from our study, found an association between parental occupation in farming and ES.[13] Other parental occupational exposures observed to be associated with childhood cancers, but not with ES specifically, include human and animal viruses, chickens, cows, other farm animals, electronics professions, fuel, oils, solvents, small and large electromagnetic fields (EMF), pesticides, organic dusts, paints, polycyclic aromatic hydrocarbons (PAHs), ionizing radiation, medical/dental professions, metals and hair dyes.[9–19]

Recently, several studies, including the current study, have reported a link between incidence of ES and elevated rates of inguinal hernia.[9,12–14,20] We hypothesized that the hernias were due to a disruption in embryological development, possibly as a result of an *in utero* parental exposure to an environmental insult, which could also have led to ES. To evaluate the developmental disruption hypothesis, we used data from Winn *et al.*[13] and developed new occupational exposure assessments to examine parental occupational exposures during the pregnancies of children who developed ES and controls. Take-home exposures may also confer risk during childhood; therefore we also examined the hypothesis that ES may result from post-pregnancy parental exposures brought home throughout childhood.[21]

Material and methods

Study design

Details of data collection have been described previously.[13] Our population of ES patients consisted of 196 children and young adults who had participated in the collaborative clinical trials of the Intergroup Ewing's Sarcoma Study from 64 institutions throughout the US.[22–24] From the original clinical trial of 274 cases, interviews were conducted with the mothers of 208 (76%) cases from 1983–1985. Parents of 63 cases were not interviewed, 32 could not be located, 10 did not speak English, 9 refused to participate, 5 had no telephone, and the remaining 7 were not interviewed for other reasons. Four additional cases were excluded from the current analysis because a person other than a biological parent was interviewed. In addition, 3 cases and their controls were excluded because we discovered they were not matched on gender, and 5 additional pairs were excluded because cases were missing hernia information, yielding 196 cases and matched controls. Both sibling and random digit dial controls originally agreed to participate; for the purposes of our study, however, only the random digit dial selected controls were used.[25] Controls were selected from the same geographical location as the cases by using the same area code and first 5 digits as the cases' phone numbers (the last 2 digits were generated randomly) and were matched to cases on gender, ethnic origin and birth date (within 2 years).[25] The cooperation rate among random digit dial controls was 92%.[26]

The telephone questionnaire administered to the mothers obtained information on medical conditions, medications and parental occupations from conception until their children's' diagnosis of ES. For controls, occupational and medical histories were censored at the age of diagnosis of the corresponding case. Information on occupation included: job title, duties, industry and dates of employment. The jobs and industries were coded using Standard Occupational Classification codes[27] and Standard Industrial Classification codes,[28] respectively.

To determine the existence of additional sources of childhood environmental exposures to pesticides, farming and animals, mothers also answered questions regarding household insect extermination, family residence on farms, involvement of their children in chores on farms and pets.

Exposure assessment

An occupational exposure expert, blinded to case status, coded the information collected on parental occupations to assess possible and probable exposures to chickens, cows, other farm animals, fuel, oils, solvents, small and large EMFs, pesticides, organic dusts, paints, PAHs, ionizing radiation, metals and hair dyes, as well as employment in electronics and medical/dental professions. These exposures were selected based on data from the literature regarding ES and other childhood cancers.[9,10,12,13,19,29–35] Parents exposed to chickens, cows and other farm animals were considered probably exposed to animal viruses. Persons in medical/dental professions and those who were likely to have had contact with large numbers of people in their occupations (*e.g.*, teachers) were considered probably exposed to human viruses. Oils were defined as lubricating, hydraulic and cutting substances. All subjects who

Dr. Prince's current address is: Albert Einstein College of Medicine, Bronx, NY, USA.

***Correspondence to:** Occupational and Environmental Epidemiology Branch, DCEG, NCI, NIH, DHHS, 6120 Executive Blvd., EPS 8118, MCS 7249, Bethesda, MD 20892-7249, USA. Fax: +301-402-1819.
E-mail: moorele@mail.nih.gov

Received 13 May 2004; Accepted after revision 16 September 2004
DOI 10.1002/ijc.20734
Published online 18 November 2004 in Wiley InterScience (www.interscience.wiley.com).

were coded as probably exposed to paints were also coded as probably exposed to solvents. Exposure to organic dusts was further divided into wood, cotton and farm-related dusts. These exposure subgroups were also rated by intensity level (low and high).

Statistical methods

Maximum likelihood estimates of the odds ratios (OR) and 95% confidence intervals (CI) were calculated by conditional logistic regression using SAS version 8.1 (SAS Institute, Inc., Cary, NC). Several variables previously associated with childhood cancer or Ewing's sarcoma were evaluated for potential confounding, including childhood diagnosis of hernia, parental smoking status during pregnancy, birth weight, maternal consumption of alcohol, caffeine, and medications during pregnancy, parental age at birth, maternal exposure to X-rays during pregnancy and childhood exposure to X-rays.[9,10,13–19] Evidence of confounding (>10% change in the OR or statistical significance at $p < 0.1$) was observed when childhood diagnosis of hernia and the smoking status of the mother during the pregnancy were included in models. All models were adjusted for these, as well as probable exposure of fathers to organic dusts during usual occupation after pregnancy, because this exposure was found to be a significant risk factor. Although this exposure was significant when both parents were analyzed together, only fathers' exposures were significantly associated with ES. Exposures that were likely to have occurred to mothers and fathers during pregnancy were analyzed separately. Parents' putative exposures that took place after the birth were combined, and also analyzed separately. For parental exposures, all children were first analyzed together, and then stratified by gender and puberty status (puberty defined as 13 years old for girls and 15 years old for boys) because previous studies hypothesized that ES incidence may be related to the growth spurt at puberty.[1,36] The results of these analyses are presented in the text only when elevated associations with ES were observed among a particular age group or gender. Similarly, residential exposures were first examined in the entire group, followed by gender and age stratification. Only exposures with at least 5 exposed subjects are presented except for organic dusts subsets when grouped by type of dust, exposure intensity and gender. All *p*-values are two-sided.

Results

Our study subjects were mostly Caucasian (94%) and male (61%). Median age of diagnosis was 13.1 years, with a range of 1.6–22.8 years. Ninety-four percent of fathers were employed during the pregnancy, and 96% were employed after pregnancy. The most common occupations held by fathers both during and after pregnancy were jobs in construction, administration/management, and mechanics. Thirty-one percent of mothers were employed during the pregnancy, primarily in administration, education, and sales. Twenty-seven percent of mothers were employed after pregnancy, most commonly in administration, education, health care and food professions.

The relationships between parental exposures during their usual occupations after the index pregnancy and ES are presented in Table I. A significantly elevated OR for ES was observed for subjects whose parents were exposed to any type of organic dust. This association increased slightly when analysis was restricted to probable exposure to organic dusts. This increase was attributable to fathers' probable exposures because only one mother (case) had probable exposure to organic dusts (all types). The association was strongest for fathers with exposures to wood dusts and again, was higher for those with probable exposure to wood dusts (OR = 3.2; 95% CI = 1.1–9.2). When intensity of exposure to wood dusts was estimated, positive associations with ES were observed (children

TABLE I – ODDS RATIOS FOR EWING'S SARCOMA IN RELATION TO PARENTAL OCCUPATIONAL EXPOSURES AFTER INDEX PREGNANCY

Exposure variable[2]	Any exposure[1]				Probable exposure only			
	OR[3]	95% CI[4]	Cases exposed	Controls exposed	OR[3]	95% CI[4]	Cases exposed	Controls exposed
Organic dusts (all types)[5]	2.1	1.0–4.2	34	20	2.4	1.1–5.3	25	13
Fathers only	2.2	1.1–4.5	33	19	2.4	1.1–5.3	25	13
Mothers only	3.5	0.4–33.0	4	1	—	—	1	0
Organic dusts (wood)[5]	2.0	0.9–4.6	22	12	3.2	1.1–9.2	16	6
Fathers	2.3	1.0–5.4	22	11	3.2	1.1–9.2	16	6
Mothers	—	—	0	1	—	—	0	0
Organic dusts (farm)[5]	2.0	0.6–6.5	12	7	1.6	0.5–4.8	11	7
Fathers only	2.0	0.6–6.5	11	7	1.6	0.5–4.8	10	7
Mothers only	—	—	1	0	—	—	1	0
Organic dusts (cotton)[5]	3.3	0.4–30.8	4	1	—	—	—	—
Fathers only	1.0	0.06–16.0	1	1	—	—	—	—
Mothers only	—	—	3	0	—	—	—	—
Pesticides	2.2	0.9–5.4	24	12	0.9	0.2–3.7	7	5
Animal viruses	0.5	0.2–1.4	14	14	1.5	0.5–4.8	12	6
Chickens	1.0	0.3–4.8	5	3	NA	NA	0	0
Cows	0.7	0.2–3.0	10	7	2.3	0.4–12.3	8	3
Other farm animals	0.9	0.3–3.3	8	5	1.1	0.1–13.6	2	1
Fuel	1.1	0.6–1.8	41	35	0.8	0.4–1.6	19	23
Oils	0.8	0.5–1.3	55	58	0.5	0.2–1.1	11	22
Polycyclic aromatic hydrocarbons	0.7	0.5–1.2	66	73	1.2	0.6–2.3	30	26
Human viruses	0.9	0.5–1.5	31	34	0.9	0.5–1.6	26	28
Medical/dental professions	1.6	0.7–4.0	13	9	1.6	0.7–4.0	13	9
Metals	0.8	0.5–1.3	63	68	1.6	0.8–3.4	24	21
Paints	0.8	0.4–1.7	29	26	0.3	0.1–1.7	2	6
Solvents	0.7	0.4–1.1	79	91	0.7	0.3–1.7	10	14

[1]Possible and probable exposure.–[2]Exposures with at least five exposed subjects are presented except organic dusts (cotton).–[3]Adjusted for childhood, diagnosis of hernia smoking status of mother during the pregnancy, and father's probable exposure to organic dusts during usual occupation after pregnancy (except for organic dust analyses).–[4]Confidence interval.–[5]Adjusted only for childhood diagnosis of hernia and mother's smoking status during the pregnancy.

of fathers with low and high exposures to wood dust had 3 times [95% CI = 0.8–11.3] and 1.5 times [95% CI = 0.6–4.3], respectively, greater odds of ES than children of fathers with no exposure [data not shown]), but no positive dose-response trend was evident. Only one mother (control) was possibly exposed to wood dust. Industries entailing probable exposure to organic dusts included carpentry, mill and lumber work (wood dust), farming (grain, hay and animal dusts), and textile manufacturing (cotton). Of parents who were exposed to organic dusts during their usual occupations, 58% were also exposed through their occupation during the pregnancies.

In addition to organic dust exposure, probable parental exposures to animal viruses, cows, to substances encountered in the medical/dental professions and to metals showed increased associations with ES (OR = ≥1.5), but none were significant. The positive relationship with ES for probable exposure to metals was seen when both younger (OR = 2.0; 95% CI = 0.6–6.3, exposed cases = 11) and older boys (OR = 3.7; 95% CI = 0.4–36.4, exposed cases = 4) were analyzed separately, as well as younger girls (OR = 3.6; 95% CI = 0.4–35.4, exposed cases = 11). Industries involving exposure to metals included aircraft manufacturing, drivers, auto and electronics maintenance and repair and welding.

Ewing's sarcoma was associated with any and probable exposure to pesticides in the crude analysis (OR = 2.7; 95% CI = 1.1–6.5 and OR = 1.5; 95% CI = 0.4–5.3, respectively), but the OR for each group decreased after controlling for fathers' exposure to all organic dusts. Exposure to pesticides occurred in farming occupations, nurseries, grocery stores and restaurants.

Probable exposure of a parent to other exposures such as PAHs and human viruses during the usual occupation were not associated with ES when all children were analyzed together. Positive associations with ES were observed among older boys whose parents were occupationally exposed to PAHs (OR = 2.4; 95% CI = 0.4–16.1, exposed cases = 6). Only younger boys had positive associations with ES when possible and probable exposure of either parent to human viruses was examined (OR = 2.4; 95% CI = 0.9–6.7, exposed cases = 16).

None of the paternal occupational exposures that occurred during pregnancy were significantly associated with ES (Table II). Organic farm dusts were non-significantly associated with about a 2-fold increased risk of ES. After stratification by gender and puberty status, increased associations with ES were only observed among older children whose fathers were exposed to any type of organic dusts during pregnancy (OR = 2.1; 95% CI = 0.7–6.1, exposed cases = 12), but this observation

TABLE II – ODDS RATIOS FOR EWING'S SARCOMA IN RELATION TO PATERNAL OCCUPATIONAL EXPOSURES DURING INDEX PREGNANCY

Exposure variable[2]	Any exposure[1]				Probable exposure only			
	OR[3]	95% CI[4]	Cases exposed	Controls exposed	OR[3]	95% CI[4]	Cases exposed	Controls exposed
Organic dusts (all types)[5]	1.3	0.7–2.3	29	22	1.4	0.7–2.8	22	16
Organic dusts (wood)[5]	1.1	0.5–2.2	17	14	1.1	0.4–2.7	11	9
Organic dusts (farm)[5]	2.2	0.7–7.2	12	7	2.2	0.7–7.2	12	7
Organic dusts (cotton)[5]	1.0	0.06–16.0	1	1	—	—	0	0
Pesticides	1.6	0.7–3.5	23	15	0.7	0.2–2.9	6	6
Animal viruses	0.7	0.2–3.1	9	7	1.6	0.3–9.2	6	3
Chickens	1.5	0.3–6.2	6	3	—	—	0	0
Cows	0.7	0.2–3.1	9	7	1.6	0.3–9.2	6	3
Other farm animals	0.9	0.2–3.6	7	5	—	—	0	1
Electronics	0.7	0.3–1.6	12	14	0.7	0.3–1.9	10	11
Ionizing radiation	1.6	0.5–3.8	9	7	0.9	0.1–14.3	1	1
Large electromagnetic fields	0.7	0.5–1.1	49	61	0.8	0.4–1.5	19	22
Small electromagnetic fields	0.8	0.5–1.3	74	76	0.7	0.4–1.4	20	25
Fuel	1.0	0.5–1.8	36	32	0.8	0.4–1.7	17	19
Oils	0.8	0.5–1.2	50	55	0.9	0.4–1.9	16	17
Polycyclic aromatic hydrocarbons	0.8	0.5–1.3	64	69	1.4	0.8–2.4	34	25
Human viruses	1.6	0.7–3.7	13	10	1.4	0.6–3.4	11	9
Medical/dental professions	6.1	0.7–50.1	6	1	6.1	0.7–50.1	6	1
Metals	0.8	0.5–1.3	56	60	0.9	0.4–1.8	20	24
Paints	0.7	0.3–1.2	23	26	0.7	0.2–3.4	3	4
Solvents	0.7	0.4–1.0	69	81	1.3	0.5–3.2	13	11

[1]Possible and probable exposure.–[2]Exposures with at least 5 exposed subjects are presented except organic dusts (cotton).–[3]Adjusted for childhood diagnosis of hernia, smoking status of mother during the pregnancy, and father's probable exposure to organic dusts during usual occupation after pregnancy (except for organic dust analyses).–[4]Confidence interval.

TABLE III – ODDS RATIOS FOR EWING'S SARCOMA IN RELATION TO MATERNAL OCCUPATIONAL EXPOSURES DURING INDEX PREGNANCY

Occupational exposure[2]	Any exposure[1]				Probable exposure only			
	OR[3]	95% CI[4]	Cases exposed	Controls exposed	OR[3]	95% CI[4]	Cases exposed	Controls exposed
Organic dusts (cotton)	1.3	0.1–18.4	3	2	—	—	0	0
Large electromagnetic fields	1.3	0.3–6.1	4	3	3.3	0.3–31.8	3	1
Small electromagnetic fields	0.9	0.6–1.6	36	34	1.2	0.5–2.9	15	11
Oils	1.2	0.3–5.3	5	3	—	—	1	0
Polycyclic aromatic hydrocarbons	0.4	0.1–1.9	3	6	0.4	0.04–4.7	1	2
Human viruses	0.4	0.2–1.0	11	18	0.5	0.2–1.1	11	16
Medical/dental professions	0.2	0.03–1.3	2	5	0.2	0.03–1.3	2	5
Metals	3.7	0.4–33.9	4	1	—	—	1	0
Solvents	1.4	0.6–3.3	16	10	—	—	2	0

[1]Possible and probable exposure.–[2]Exposures with at least 5 exposed subjects are presented.–[3]Adjusted for childhood diagnosis of hernia, smoking status of mother during the pregnancy, and father's probable exposure to organic dusts during usual occupation after pregnancy (except for organic dust analyses).–[4]Confidence interval.

was not confirmed when analysis was limited to only those with probable exposure.

Other elevated but non-significant associations with ES (OR = ≥1.5) were observed among children of fathers who had been exposed to pesticides, chickens, human viruses, and who were exposed to substances used in medical or dental professions. The association with pesticides was primarily observed among younger boys (OR = 6.5; 95% CI = 0.6–76.2, exposed cases = 6), and exposure to PAHs increased odds of ES among younger boys and girls combined (OR = 1.7; 95% CI = 0.8–3.5, exposed cases = 22). The OR for probable paternal exposure to human viruses during pregnancy showed a slightly increased association with ES for younger girls (OR = 4.9; 95% CI = 0.5–47.1, exposed cases = 4). Children diagnosed with ES before puberty whose fathers were exposed to fuel (OR = 1.8; 95% CI = 0.7–4.4, exposed cases = 22) and solvents during the pregnancy (OR = 1.9; 95% CI = 0.6–6.1, exposed cases = 9) also had positive associations with ES.

Table III presents OR estimates for ES in relation to maternal exposures during pregnancy. None of the exposures were significantly associated with ES. The low prevalence of women employed outside of the home during pregnancy resulted in a small number of occupationally exposed women for analysis. Maternal exposures to large EMFs and metals during pregnancy showed positive associations with ES (OR = ≥1.5), whereas exposure to PAHs, human viruses and medical/dental professions showed negative associations. When analyses were restricted to probable exposures or by certain age and gender strata, the number of exposed subjects became too small to conduct meaningful analyses.

An analysis of additional childhood exposures found that household pest extermination during childhood was significantly associated with ES in younger boys (OR = 3.0; 95% CI = 1.1–8.1, exposed cases = 25) but not in girls or older boys (Table IV). Combining children whose parents had exposure to pesticides during their usual occupations with children whose houses had received pesticide extermination treatments, the risk of ES was increased (OR = 1.5; 95% CI = 0.9–2.5, exposed cases = 80), particularly among younger boys (OR = 3.4; 95% CI = 1.2–9.3, exposed cases = 30). When this combined analysis was stratified for older boys and both age classifications of girls, significant positive associations with ES were not observed (data not shown).

Younger boys and older girls had a non-significant elevated association with ES if they always lived on a farm, but this exposure was protective for older boys. Ever living on a farm was a risk factor for both age groups of girls (combined OR = 3.1, 95% CI = 0.8–11.8, exposed cases = 16). Having carried out chores on the farm was associated with a reduced risk of ES for both age groups of boys and for older girls.

In both age groups of boys, as well as older girls, positive associations with ES were observed if they had pets in the household during childhood. When all children with pets were combined, the OR was 1.6 (95% CI = 0.9–2.7). Boys who had household pets during childhood or who had parents that were exposed to chickens, cows or other farm animals during their usual occupations had positive associations with ES (OR = 2.3; 95% CI = 1.1–4.7; exposed cases = 103).

TABLE IV – RESIDENTIAL EXPOSURES AND ODDS RATIO FOR EWING'S SARCOMA BY GENDER AND AGE AT DIAGNOSIS

Exposure[1]	Boys 15 and younger (n = 144)			Boys older than 15 (n = 98)			Girls 13 and younger (n = 84)			Girls older than 13 (n = 66)		
	OR[2] (95% CI[3])	Cases exposed	Controls exposed	OR[2] (95% CI[3])	Cases exposed	Controls exposed	OR[2] (95% CI[3])	Cases exposed	Controls exposed	OR[2] (95% CI[3])	Cases exposed	Controls exposed
Household extermination during childhood	3.0 (1.1–8.1)	25	16	0.8 (0.3–2.1)	13	16	1.1 (0.4–3.2)	11	11	1.2 (0.2–6.1)	9	7
Always lived on a farm	2.3 (0.4–12.3)	8	4	0.2 (0.01–2.6)	3	4	—	2	3	1.7 (0.2–15.4)	4	4
Ever lived on a farm	0.9 (0.4–2.2)	16	14	0.6 (0.1–2.4)	11	11	6.4 (0.7–58.4)	7	4	2.7 (0.5–15.3)	9	5
Performed farm chores	0.4 (0.1–2.0)	5	7	0.2 (0.02–1.4)	5	9	1.5 (0.3–9.0)	4	3	0.3 (0.03–3.2)	2	4
Pets in household during childhood	1.8 (0.8–3.9)	56	46	3.1 (0.6–16.3)	44	40	0.8 (0.3–2.3)	26	29	2.6 (0.5–13.6)	31	27

[1]Only exposures with at least 5 exposed subjects are presented.–[2]OR adjusted for childhood diagnosis of hernia, father's exposure to organic dusts during usual occupation, and mother smoking during pregnancy.–[3]Confidence interval.

Discussion

Our study found ES that is significantly associated with any or probable parental occupational exposure to organic dusts during usual occupation after pregnancy. The association increased when analysis was limited to probable exposure, strengthening the evidence that organic dusts may be risk factors for ES. Furthermore, positive associations were also present across gender and age strata, though the precision of estimates was limited by small numbers of exposed subjects. Evaluation by specific type of organic dust exposure and ES revealed associations with parental

exposure to both farm and wood dusts, but only exposure to wood dusts was statistically significant. Similar to the pattern observed for total organic dust exposure, the association was stronger when analysis was limited to include probable wood dust exposure. Although the intensity of exposure did not show a consistent upward trend in odds ratios, the wide confidence limits around these indicate they are unstable due to small numbers of exposed subjects ($n = 34$ exposed subjects).

Wood dust is considered a known human carcinogen (Group 1) based on evidence from epidemiologic studies.[37,38] Strong and consistent associations between wood dust exposure with adenocarcinoma of the nasal cavities and paranasal sinuses have been observed. Wood dusts have also been shown to damage DNA in cells that are not directly exposed to dust particulate itself. For example, wood dust exposure has been associated with an increased prevalence of DNA damage (single strand breaks)[37] and micronuclei[39] in peripheral lymphocytes from occupationally exposed individuals. Toxicologic analysis of certain wood dust extracts has shown that some of the naturally occurring chemicals in woods have both mutagenic and chromosome damaging properties.[37,38] Although the exact mechanism through which dusts could cause Ewing's sarcoma in children is uncertain, this evidence indicates that wood dust exposure could have health effects at sites distant from the point of entry.

Previous studies have associated parental occupation on a farm with ES.[9–12] Holly *et al.*[9] found an elevated risk for ES in children whose fathers had agricultural occupations from 6 months before conception until the time of diagnosis. Hum *et al.*[10] reported that children of mothers who worked in the farming industry before conception and during pregnancy were at almost 8-fold greater risk of ES. Valery *et al.*[12] determined that children whose mothers or fathers worked on farms around the time of conception (particularly in cases <20 years old at diagnosis) were at twice the risk of having ES than children of non-farming parents, but these findings were based on small numbers of exposed subjects and risks were not significant. Previously published results from our study indicated that children of fathers employed in farming occupations at time of pregnancy were at around a 2-fold risk of ES compared to children whose fathers had other occupations.[13] Some non-significant relationships between childhood farm residence and ES were also observed, especially for younger boys who had always lived on a farm and girls of both age groups who had ever lived on a farm.

Holly *et al.*[9] also reported a significantly elevated risk ratio in children whose fathers were exposed to herbicides, pesticides or fertilizers at any time during their occupations. In our current study, crude OR were significantly elevated for pesticide exposure, but the associations weakened after controlling for fathers' exposures to organic dusts, which included farm dusts. Associations with other farm related exposure, such as animal viruses, chickens, cows and other farm animals also decreased after controlling for organic dust exposure.

Some researchers have hypothesized that the etiology of ES is infectious. Holman et al.[11] described 6 male ES cases diagnosed between 12–28 years old, living in rural Australia, all of whom had at least some direct contact with farm animals, and 2 had direct contact with each other. In our study, associations with potential exposure to animal viruses were observed among younger boys, but the number of exposed older boys was too small for meaningful analysis. Household pet exposure also showed increased but nonsignificant associations with ES. Household pets and farm animal exposure showed significantly elevated associations with ES in all boys. In future studies of ES, childhood animal exposure warrants further investigation. The relationship between parental exposures to human viruses and ES was inconsistent. Chance, small numbers of exposed subjects and exposure misclassification may be responsible for these inconsistent results.

Certain non-farming occupational exposures have also been associated with ES. Valery *et al.*[12] found risk doubled for those subjects whose fathers had ever handled solvents, glues, oils and greases. In contrast, we found possible or probable exposure of either parent to solvents during their usual occupations showed decreased associations with ES.

This is one of the largest case-control studies focusing exclusively on the etiology of ES to date. By differentiating exposures that took place during pregnancy from those that took place during usual occupations after pregnancy, we attempted to distinguish among exposures that may have led to ES as a result of a disturbance *in utero* from those that occurred during childhood.

Our evaluation of residential exposures as well as parental occupational exposures allowed us to combine similar exposures from multiple sources to improve exposure assessment accuracy, although we were not able to account for non-occupational or non-residential sources of exposure. The relative magnitude of outside sources of exposure is believed to be small, and geographical matching of cases and controls reduced confounding by ecologic exposures. The possibility remains, however, that unaccounted burdens of exposure may have contributed to ES development.

Recall bias may also be a significant limitation in our study. The rarity of childhood cancers limits researchers' abilities to eliminate recall bias by implementing a cohort study design. Parents of cases may have been more inclined to remember and report exposures as an effort to explain their children's cancers. Studies investigating the effects of recall bias generally have found that although cases and controls both underreport past exposures, reporting has been non-differential with regard to case status,[40–49] although case parents have been found to be more likely to volunteer information about exposures they suspect may have contributed to cancer in their children.[50] The tendency of case parents to volunteer unasked information is unlikely to have been relevant in our study because rather than ask parents about specific exposures, we collected occupational histories, which are less susceptible to recall bias. To gain a more specific understanding of workplace exposures, we reviewed the information collected describing each subjects' specific jobs, and experts, blind to case status, assigned a selection of possible and probable occupational exposures. Such an approach is more accurate than a job exposure matrix, which assigns the same exposure status to all individuals with the same job/industry combination, and therefore decreases the inherent variability among the job/industry combinations. The possibility exists, however, that erroneous exposure assignments could have resulted as a consequence of using exposure information that often lacked important determinants of exposure.

Another limitation of our study is the use of mothers as proxies for data on paternal occupational history. Because histories were not obtained from the fathers themselves, misclassification of occupational exposures could have occurred, and interviews with the fathers would have probably provided a more accurate assessment of their occupational exposures.[51] Agreement rates between mothers' and fathers' reporting of paternal job history were fairly similar, however, when cases were compared to controls.[51] Furthermore, agreement between maternal and paternal reporting is higher when occupational history, rather than specific exposures, are queried.[52–55]

To thoroughly evaluate the occupational exposures in this cohort, many comparisons were computed for these analyses, raising the possibility that some of the findings reported may have been significant by chance. Additional studies will be necessary to confirm our results.

Finally, the cases involved in our study were initially identified on the basis of the locations of their treatments, and therefore neither they nor the geographically-matched controls are representative of the population of the United States as a whole. Because cases were also excluded from our study for a variety of reasons, the results of these analyses cannot be extrapolated to a population level.

In conclusion, the results of our study suggest that earlier reports relating parental farm employment and ES may have been describing risk associated with organic dusts encountered when working on a farm, rather than other agricultural or farming exposures. Further studies should focus on involving greater numbers of exposed subjects and on targeting populations with greater prevalence of exposure to organic dusts, pesticides, and human and animal viruses. More detailed questionnaires should be used to obtain more specific exposure information (*vs.* broad classes of exposure).[56] At the time these parents were interviewed (early 1980s), it was not common for women to work during or after pregnancy, resulting in few occupational exposures.[57,58] Given that more women today continue to work well into their pregnancies and return to work shortly after childbirth, new studies of parental exposures and ES are warranted.

Acknowledgements

We thank Drs. J. Cope and D. Winn for their participation and scientific contributions to our study.

References

1. Ries LAG, Smith MA, Gurney JG, Linet M, Tamra T, Young JL, Bunin GR. Cancer incidence and survival among children and adolescents: United States SEER Program 1975–1995. Bethesda, MD: National Cancer Institute, 1999.
2. West DC. Ewing sarcoma family of tumors. Curr Opin Oncol 2000; 12:323–9.
3. Miller RW. Etiology of childhood bone cancer: epidemiologic observations. Recent Results Cancer Res 1976;54:50–62.
4. Glass AG, Fraumeni JF Jr. Epidemiology of bone cancer in children. J Natl Cancer Inst 1970;44:187–99.
5. Cavazzana AO, Miser JS, Jefferson J, Triche TJ. Experimental evidence for a neural origin of Ewing's sarcoma of bone. Am J Pathol 1987;127:507–18.
6. Cope JU. A viral etiology for Ewing's sarcoma. Med Hypotheses 2000;55:369–72.
7. Fraumeni JF Jr, Glass AG. Rarity of Ewing's sarcoma among U.S. Negro children. Lancet 1970;141:366–7.
8. Young JL Jr, Miller RW. Incidence of malignant tumors in U.S. children. J Pediatr 1975;86:254–8.
9. Holly EA, Aston DA, Ahn DK, Kristiansen JJ. Ewing's bone sarcoma, paternal occupational exposure, and other factors. Am J Epidemiol 1992;135:122–9.
10. Hum L, Kreiger N, Finkelstein MM. The relationship between parental occupation and bone cancer risk in offspring. Int J Epidemiol 1998;27:766–71.
11. Holman CD, Reynolds PM, Byrne MJ, Trotter JM, Armstrong BK. Possible infectious etiology of six cases of Ewing's sarcoma in Western Australia. Cancer 1983;52:1974–6.
12. Valery PC, McWhirter W, Sleigh A, Williams G, Bain C. Farm exposures, parental occupation, and risk of Ewing's sarcoma in Australia: a national case-control study. Cancer Causes Control 2002;13: 263–70.
13. Winn DM, Li FP, Robison LL, Mulvihill JJ, Daigle AE, Fraumeni JF Jr. A case-control study of the etiology of Ewing's sarcoma. Cancer Epidemiol Biomarkers Prev 1992;1:525–32.
14. Cope JU, Tsokos M, Helman LJ, Gridley G, Tucker MA. Inguinal hernia in patients with Ewing sarcoma: a clue to etiology. Med Pediatr Oncol 2000;34:195–9.
15. Alexander FE. Viruses, clusters and clustering of childhood leukaemia: a new perspective? Eur J Cancer 1993;29A:1424–43.
16. Greaves MF. Aetiology of acute leukaemia. Lancet 1997;349: 344–9.
17. Ji BT, Shu XO, Linet MS, Zheng W, Wacholder S, Gao YT, Ying DM, Jin F. Paternal cigarette smoking and the risk of childhood cancer among offspring of nonsmoking mothers. J Natl Cancer Inst 1997 Feb 5;89(3):238–44.
18. Savitz DA, Chen JH. Parental occupation and childhood cancer: review of epidemiologic studies. Environ Health Perspect 1990;88: 325–37.
19. Shu XO, Stewart P, Wen WQ, Han D, Potter JD, Buckley JD, Heineman E, Robinson LL. Parental occupational exposure to hydrocarbons and risk of acute lymphocytic leukemia in offspring. Cancer Epidemiol Biomarkers Prev 1999 Sep;8(9):783–91.
20. Valery PC, McWhirter W, Sleigh A, Williams G, Bain C. A national case-control study of Ewing's sarcoma family of tumours in Australia. Int J Cancer 2003;105:825–30.
21. McDiarmid MA, Weaver V. Fouling one's own nest revisited. Am J Ind Med 1993;24:1–9.
22. Burgert EO Jr, Nesbit ME, Garnsey LA, Gehan EA, Herrmann J, Vietti TJ, Cangir A, Tefft M, Evans R, Thomas P, et al. Multimodal therapy for the management of nonpelvic, localized Ewing's sarcoma of bone: intergroup study IESS-II. J Clin Oncol 1990 Sep;8(9):1514–24.
23. Evans RG, Nesbit ME, Gehan EA, et al. Multimodal therapy for the management of localized Ewing's sarcoma of pelvic and sacral bones: a report from the second intergroup study. J Clin Oncol 1991;9:1173–80.
24. Nesbit ME Jr, Gehan EA, Burgert EO Jr, Vietti TJ, Cangir A, Tefft M, Evans R, Thomas P, Askin FB, Kissane JM, et al. Multimodal therapy for the management of primary, nonmetastatic Ewing's sarcoma of bone: a long-term follow-up of the First Intergroup study. J Clin Oncol 1990 Oct;8(10):1664–74.
25. Robison LL, Daigle A. Control selection using random digit dialing for cases of childhood cancer. Am J Epidemiol 1984;120:164–166.
26. Daigle AE. Epidemiologic study of etiologic factors in Ewing's sarcoma. vol. I, II. Childhood cancer. University of Minnesota, 1986.
27. U. S. Department of Commerce (1980). Standard Occupational Classification Manual, Washington, DC: Office of Federal and Statistical Policy and Standards.
28. Office of Management and Budget. Standard Industrial Classification Manual, 1972. Washington, DC: Bernan Press, 1972.
29. Daniels JL, Olshan AF, Savitz DA. Pesticides and childhood cancers. Environ Health Perspect 1997;105:1068–77.
30. Freedman DM, Stewart P, Kleinerman RA, Wacholder S, Hatch EE, Tarone RE, Robison LL, Linet MS. Household solvent exposures and childhood acute lymphoblastic leukemia. Am J Public Health 2001 Apr;91(4):564–7.
31. Holly EA, Bracci PM, Mueller BA, Preston-Martin S. Farm and animal exposures and pediatric brain tumors: results from the United States West Coast Childhood Brain Tumor Study. Cancer Epidemiol Biomarkers Prev 1998;7:797–802.
32. Johnson CC, Spitz MR. Childhood nervous system tumours: an assessment of risk associated with paternal occupations involving use, repair or manufacture of electrical and electronic equipment. Int J Epidemiol 1989;18:756–62.
33. Knox EG, Gilman EA. Hazard proximity of childhood cancers in Great Britain from 1953–80. J Epidemiol Community Health 1997; 51:151–9.
34. Martini F, Lazzarin L, Iaccheri L, Corallini A, Gerosa M, Trabanelli C, Calza N, Barbanti-Brodano G, Tognon M. Simian virus 40 footprints in normal human tissues, brain and bone tumours of different histotypes. Dev Biol Stand 1998;94:55–66.
35. Sanchez-Prieto R, de Alava E, Palomino T, Guinea J, Fernandez V, Cebrian S, LLeonart M, Cabello P, Martin P, San Roman C, Bornstein R, Pardo J, Martinez A, Diaz-Espada F, Barrios Y, Ramon y Cajal S. An association between viral genes and human oncogenic alterations: the adenovirus E1A induces the Ewing tumor fusion transcript EWS-FLI1. Nat Med 1999 Sep;5(9):1076–9.
36. Buckley JD, Pendergrass TW, Buckley CM, Pritchard DJ, Nesbit ME, Provisor AJ, Robison LL. Epidemiology of osteosarcoma and Ewing's sarcoma in childhood: a study of 305 cases by the Children's Cancer Group. Cancer 1998 Oct 1;83(7):1440–8.
37. IARC International Agency for Research on Cancer. Wood Dust, IARC monographs on the evaluation of carcinogenic risk to humans. Vol. 62. Lyon, France: IARC, 1995, p. 35–215.
38. National Toxicology Program. NTP Chemical Repository, Wood Dust. 2004. http:/ehp.niehs.nih.gov/roc/tenth/profiles/s189wood.pdf.
39. Jiang ZC, Su YL, Zhang J, Deng YF, Ma ZH, Dong QL. Study on micronucleus frequency in peripheral lymphocytes in workers of match factories. Biomed Environ Sci 1994;7:150–3.
40. Berwick M, Chen YT. Reliability of reported sunburn history in a case-control study of cutaneous malignant melanoma. Am J Epidemiol 1995;141:1033–7.
41. Chouinard E, Walter S. Recall bias in case-control studies: an empirical analysis and theoretical framework. J Clin Epidemiol 1995;48: 245–54.
42. Delgado-Rodriguez M, Gomez-Olmedo M, Bueno-Cavanillas A, Garcia-Martin M, Galvez-Vargas R. Recall bias in a case-control study of low birth weight. J Clin Epidemiol 1995;48:1133–40.
43. Friedenreich CM, Howe GR, Miller AB. Recall bias in the association of micronutrient intake and breast cancer. J Clin Epidemiol 1993;46: 1009–17.
44. Giovannucci E, Stampfer MJ, Colditz GA, Manson JE, Rosner BA, Longnecker MP, Speizer FE, Willett WC. Recall and selection bias in

reporting past alcohol consumption among breast cancer cases. Cancer Causes Control 1993 Sep;4(5):441–8.
45. Holmberg L, Ohlander EM, Byers T, Zack M, Wolk A, Bruce A, Bergstrom R, Bergkvist L, Adami HO. A search for recall bias in a case-control study of diet and breast cancer. Int J Epidemiol 1996 Apr;25(2):235–44.
46. Kerber RA, Slattery ML. Comparison of self-reported and database-linked family history of cancer data in a case-control study. Am J Epidemiol 1997;146:244–8.
47. Mackenzie SG, Lippman A. An investigation of report bias in a case-control study of pregnancy outcome. Am J Epidemiol 1989;129: 65–75.
48. Roberts I. Differential recall in a case-control study of child pedestrian injuries. Epidemiology 1994;5:473–5.
49. Roeleveld N, Kiemeney L, Schattenberg G, Peer P. Information bias in a case-referent study on mental retardation and parental occupation: colleagues as dual respondents. Epidemiology 1990;1:292–7.
50. Teschke K, Smith JC, Olshan AF. Evidence of recall bias in volunteered vs. prompted responses about occupational exposures. Am J Ind Med 2000;38:385–8.
51. Schnitzer PG, Olshan AF, Savitz DA, Erickson JD. Validity of mother's report of father's occupation in a study of paternal occupation and congenital malformations. Am J Epidemiol 1995; 141:872–7.
52. Boyle CA, Brann EA. Proxy respondents and the validity of occupational and other exposure data. The Selected Cancers Cooperative Study Group. Am J Epidemiol 1992;136:712–21.
53. Johnson RA, Mandel JS, Gibson RW, Mandel JH, Bender AP, Gunderson PD, Renier CM. Data on prior pesticide use collected from self- and proxy respondents. Epidemiology 1993 Mar;4(2):157–64.
54. Lerchen ML, Samet JM. An assessment of the validity of questionnaire responses provided by a surviving spouse. Am J Epidemiol 1986;123:481–9.
55. Shalat SL, Christiani DC, Baker EL Jr. Accuracy of work history obtained from a spouse. Scand J Work Environ Health 1987;13:67–9.
56. Stewart PA, Stewart WF, Heineman EF, Dosemeci M, Linet M, Inskip PD. A novel approach to data collection in a case-control study of cancer and occupational exposures. Int J Epidemiol 1996;25:744–752.
57. Wagener DK, Walstedt J, Jenkins L, Burnett C, Lalich N, Fingerhut M. Women: work and health. Vital Health Stat 3 1997;1–91.
58. Bureau of Labor Statistics. Employment and Earnings Report, 1997. Washington, DC: US Government Printing Office, 1998.